

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Michael BUSCHLE *et al.*

Serial No.: 10/564,429

Filed: April 24, 2006

For: HCV VACCINES

Group Art Unit: 1648

Examiner: Z. Lucas

Atty. Dkt. No.: SONN:084US

Confirmation No.: 7323

DECLARATION OF DR. HANS HEINRICH WEDEMEYER

I, Dr. Hans Heinrich Wedemeyer, declare as follows:

1. I am a German citizen, and my place of residence is Hannover, Germany.

2. I am a medical doctor with the Department of Gastroenterology and Hepatology at Medizinische Hochschule, located in Hannover, Germany. I am currently a member of the Research Group at Medizinische Hochschule concerning Phase II clinical trials for an HCV vaccine named "IC41." A copy of my *curriculum vitae* is attached as Appendix A.

3. I have reviewed the specification, and the current claims related to the above-referenced U.S. patent application.

4. The HCV vaccine, IC41, involved in the Phase II clinical trials at Medizinische Hochschule contains the following HCV peptides: Ipep 83, Ipep 84, Ipep 87, Ipep 89, and Ipep 1426. These peptides are described in the specification and recited in the current claims of the above-referenced patent application as SEQ ID NOs: 72, 60, 19, 17, and 63, respectively. In addition to the HCV epitopes, the IC41 vaccine also contains poly-L-arginine as an adjuvant.

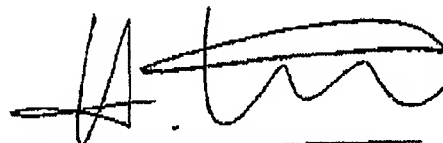
5. I am providing this declaration to present additional data showing that IC41 is therapeutically effective in treating human patients infected with HCV genotype 1. These data result from an interim analysis of ongoing phase II clinical trials for IC41. Attached as Appendix 2 is a detailed Data Sheet explaining these data.

6. The Data Sheet provides data concerning a clinical trial of 50 human patients with chronic hepatitis C, genotype 1, naïve to treatment and positive for HLA-A2. These patients received 8 intra dermal vaccinations of IC41 (i.e., 2.5 mg/ml peptides adjuvanted with 2 mg/ml poly-L-arginine) in bi-weekly intervals (see Tables 1 and 2 of Data Sheet for corresponding data). Each vaccination was followed by the topical application of one dose of Aldara™ (imiquimod).

7. To assess the therapeutic efficacy of IC41 vaccination, each patient's viral load was quantified by measuring HCV RNA levels prior to receiving any IC41 vaccination (baseline) and prior to each subsequent IC41 vaccination. Follow up HCV RNA quantifications were performed two weeks and twenty-four weeks after the last IC41 vaccination. The IC41 vaccination regimen resulted in a statistically significant decline of HCV RNA load in 92% of the patients (i.e., 46 patients) by week 12 (see Table 1 of the Data Sheet). Interestingly, the apparent antiviral effect was more pronounced in patients with high viral load (> 2000000 U/mL) compared to patients with low viral load (≤ 2000000 U/mL). A statistically significant decline in HCV RNA could be seen at week 8 when the data from high viral load patients were analyzed separately (see Table 2 of the Data Sheet). Based on my experience in the study of HCV infections, I find that such a reduction in HCV RNA load in patients equates to a therapeutically effective response from the IC41 vaccine.

I declare that all statements made of my knowledge are true and all statements made on the information are believed to be true; and, further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereupon.

Date: Apr. - 28 - 2008


Dr. Hans Heinrich Wedemeyer

APPENDIX A
(*Curriculum Vitae*)

Curriculum Vitae

Personal Details:

Name: Dr. Hans Heinrich Wedemeyer
Date of birth: April 10th, 1967
Place of birth: Göttingen, Germany
Nationality: German
Address: Hannover Medical School
Dept. Gastroenterology, Hepatology and Endocrinology
Carl Neuberg Str. 1
D-30625 Hannover

EDUCATION:

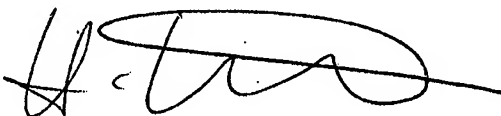
July 2000 to present: Dept. of Gastroenterology and Hepatology
Medizinische Hochschule Hannover, Germany
May 1998 to June 2000: Research-Fellowship
Liver Diseases Section, NIDDK, NIH,
Bethesda, MD, USA
funded by a grant from the Deutsche Forschungsgemeinschaft (WE-2431-1)
May 1996 to May 1998: Dept. of Gastroenterology and Hepatology
Medizinische Hochschule Hannover, Germany
Doctor of Medicine: 02-Jul-1996
State license as Physician: 22-Apr-1996
University education: October 1988 until April 1996 at the Georg-August University in
Göttingen
(medicine and music)
Community service: 10/1986 - 5/1988 with the St. John's Ambulance Brigade in
Göttingen (care of totally disabled people)

RESEARCH EXPERIENCE:

1991-1995 Institute for sensory and neurophysiology,
Georg August University, Göttingen
Prof. Dr. Dr. D. Schild
1996-1998 Dept. of Gastroenterology and Hepatology
Medizinische Hochschule Hannover
Prof. Dr. M. P. Manns
1998-2000 Liver Diseases Section, NIDDK, NIH,
Bethesda, MD, USA
Dr. B. Rehermann, Dr. T.J. Liang
2000-present Research Group Leader (Principal Investigator)
in the Dept. of Gastroenterology and Hepatology, Medizinische Hochschule
Hannover, Germany: Cellular Immunology in Viral Hepatitis
Investigator in >20 trials in the field of viral hepatitis (Phase I-IV)
Principal Investigator in several clinical trials (>10 trials)
Scientific secretary German Network of Competence on Viral Hepatitis

Hannover,

20.10.06



APPENDIX 2
(Data Sheet Concerning IC41 Vaccine Phase II Clinical Trial)

DATA SHEET FOR IC41 VACCINE PHASE II HUMAN CLINICAL TRIALS

Example I: significant decline of HCV RNA in chronic HCV genotype 1 patients naïve to standard therapy after vaccination with IC41

In an open label, multicenter phase 2 clinical trial 50 patients with chronic hepatitis C, genotype 1, naïve to treatment and positive for HLA-A2 were enrolled in 8 centers in Romania, Poland and Germany. Patients received 8 intra dermal vaccinations of IC41 (0,5 ml formulation H, i.e. 2,5 mg/ml peptides adjuvanted with 2 mg/ml poly-L-arginine) in bi-weekly intervals; each vaccination was followed by topic application of one dose of Aldara™ crème containing the TLR7 agonist imiquimod.

HCV RNA was quantified with the Cobas Ampliprep / Cobas TaqMan HCV 48 (Roche Diagnostics) test at baseline prior to any IC41 vaccination and prior to each subsequent vaccination. Follow up HCV RNA quantifications were done two weeks and twenty four weeks after the last vaccination.

HCV RNA data of 46 patients (intent to treat population) for all time points until two weeks after the last vaccination were analysed by an interim analysis, as well as the HCV RNA data of those 43 patients, who fulfilled all the criteria of the clinical study protocol (per protocol population).

This interim analysis showed a statistically significant decline of HCV RNA in 46 patients (intent to treat population) from the baseline until two weeks after the last IC41 vaccination. The decline was 0.1952 IU/mL, $p = 0.0010$ with a 95 % confidence interval of 0.0752; 0.2152. This result was confirmed in 43 patients of the per protocol population. The decline was 0.2008 IU/mL, $p = 0.0009$ with a 95 % confidence interval of 0.0787; 0.3228.

To get additional confidence in the data an additional analysis of the very first visit up to roughly 30 days earlier than the baseline visit was done. This supportive analysis showed a statistically significant decline of HCV RNA in 46 patients (intent to treat population) from the baseline until two weeks after the last IC41 vaccination. The decline was 0.1798 IU/mL, $p = 0.0088$ with a 95 % confidence interval of 0.0334; 0.3262. This result was confirmed in 43 patients of the per protocol population. The decline was 0.2142 IU/mL, $p = 0.0015$ with a 95 % confidence interval of 0.0777; 0.3507. For HCV RNA decline in a two weeks interval over time see Table 1.

Table 1
(HCV RNA Decline Per Visit in Relation to the Baseline—*i.e.*, Pre-Vaccination Visit)

| Logarithmic HCV Load [IU/mL] – Change between Baseline V1 and each individual visit (ITT Set: 46 patients) | | | |
|---|-----------------------|--|------------------------------------|
| | Point Estimate | p value (one-sided) $\alpha = 0.025$ | Confidence Interval 95% |
| V1-V2 (wk2) | -0.0197 | 0.6355 | [-0.1340, 0.0945] |
| V1-V3 (wk4) | -0.0129 | 0.5909 | [-0.1258, 0.0999] |
| V1-V4 (wk6) | 0.0625 | 0.1401 | [-0.0528, 0.1778] |
| V1-V5 (wk8) | 0.0919 | 0.0946 | [-0.0470, 0.2309] |
| V1-V6 (wk10) | 0.1147 | 0.0591 | [-0.0304, 0.2598] |
| V1-V7 (wk12)* | 0.1879 | 0.0021 | [0.0628, 0.3130] |
| V1-V8 (wk14)* | 0.3472 | 0.0002 | [0.1678, 0.5265] |
| V1-V9 (wk16)* | 0.1952 | 0.0010 | [0.0752, 0.3152] |

*Denotes statistically significant decline in HCV RNA load in patient

Interestingly, the apparent antiviral effect was more pronounced in patients with high viral load (> 2000000 U/mL) compared to patients with low viral load (\leq 2000000 U/mL). In patients with low viral load the HCV RNA decrease did not reach statistical significance. For HCV RNA decline in a two weeks interval over time in patients with high viral load see Table 2.

Table 2
(HCV RNA Decline Per Visit in Relation to the Baseline—*i.e.*, Pre-Vaccination Visit in Patients with High Viral Load)

**Logarithmic HCV Load [IU/mL] for high baseline HCV RNA
(ITT Set; 25 patients)**

| | Point Estimate | p value (one-sided) $\alpha = 0.025$ | Confidence Interval 95% |
|----------------------|-----------------------|--|------------------------------------|
| V1-V2 (wk2) | 0.0524 | 0.2387 | [-0.0979, 0.2026] |
| V1-V3 (wk4) | 0.0498 | 0.2298 | [-0.0876, 0.1871] |
| V1-V4 (wk6) | 0.1194 | 0.0282 | [-0.0035, 0.2423] |
| V1-V5 (wk8)* | 0.2337 | 0.0049 | [0.0623, 0.4051] |
| V1-V6 (wk10)* | 0.2271 | 0.0033 | [0.0701, 0.3842] |
| V1-V7 (wk12)* | 0.2657 | 0.0002 | [0.1310, 0.4004] |
| V1-V8 (wk14)* | 0.5215 | 0.0001 | [0.2803, 0.7627] |
| V1-V9 (wk16)* | 0.3246 | 0.0002 | [0.1641, 0.4850] |

*Denotes statistically significant decline in HCV RNA load in patient